REMARKS

Claims 1 through 3, 6, 8, 10 through 15 and 19 through 24 are pending in the above-referenced application.

Applicants acknowledge with gratitude the Examiner's indication that Claims 20 through 22 are patentable in light of the art of record.

Claims 20 and 21 have been amended to remove the reference to 20-arm polyethylene polyethylene glycol polymer.

Claims 20 and 21 have been further amended to reflect that in advantageous embodiments, 13-arm, 18-arm or 24-arm polyethylene glycol polymer may be used. Support for this amendment can be found in the Application-as-filed on Pages 20 to 22, Examples 27 to 54.

Claim 14 and 15 have been canceled solely to advance prosecution of the above referenced case, as required in Paragraph 14 of the outstanding Office Action. Applicants respectfully submit that Claims 14 and 15 have been canceled without prejudice or disclaimer to the filing of continuing applications thereon.

Applicants respectfully submit that this response does not raise new issues, but merely places the above-referenced application either in condition for allowance, or alternatively, in better form for appeal. Reexamination and reconsideration of this application, withdrawal of all rejections, and formal notification of the allowability of the pending claims are earnestly solicited in light of the remarks which follow.

The Claimed Invention is Patentable in light of 35 USC 112

Claims 1 through 3, 6, 8, 10 through 13 and 19 through 24 stand rejected over the phrase "further comprising a moiety $[A^-]_w$." The Application-as-filed at Page 5, lines 15 through 24, clearly indicate that the polyethyleneimine moiety "B" advantageously includes a group $[A^-]_w$. The Application-as-filed then goes on to define (i) "A^-" as an equivalent of an anion at Page 6, line 1 and (ii) "w" as an integer chosen to balance positive charges on Page 6, lines 15 through 16. Applicants thus respectfully submit that the Application-as-filed conveyed with reasonable clarity to one skilled in the art that Applicants were in possession of the claimed invention as of the filing date sought. Applicants further respectfully submit that the subject matter of the claims need not be described literally within the remainder of the specification, i.e. word-for-word correspondence is not required. MPEP 2163.02. Accordingly, Applicants respectfully request withdrawal of the foregoing rejection.

Applicants' Representative further respectfully submits that if the foregoing rejection instead reflects a lack of clarity over the use of "A" as a moiety identifier to mean a hydrophilic polymer and "A^-" as a moiety identifier to mean an equivalent of an anion, then Applicants would be pleased to substitute a different moiety identifier for "A^-."

Claims 1, 2, 6, 8, 10, 11, 13, 19, 20, 23 and 24 presumably stand rejected over the phrase " p = 1 and 3 - 10." As correctly noted by the Examiner, the Application-as-filed on Page 3, line 5 notes that "p" may range from 1 to 10 and further that p may be 3. Accordingly, Applicants thus respectfully submit that the Application-as-filed clearly conveys with reasonable clarity to one skilled in the art that Applicants were in possession of the claimed invention as of the filing date sought. More specifically, one skilled in the art would consider the claimed lower end points of 1 and 3 and upper end point of 10 to be expressly supported by the discussion in the original disclosure. Applicants further respectfully submit that one skilled in the art would consider the

claimed range supported by the original disclosure in conformance with *In re Wertheim*, 541 F.2d 257 (CCPA 1976) (MPEP 2163.05). Accordingly, Applicants respectfully request withdrawal of the foregoing rejection.

Claims 1 through 3, 6, 8, 10 through 13 and 19 through 24 presumably stand rejected over the phrase " 5 000 to 10 000 000 g/mole." As correctly noted by the Examiner, the Application-as-filed notes that linear polymers suitable for use in the instant invention may have a molecular weight ranging from 100 to 10 000 000 g/mol, as described in the Application-as-filed on Page 2, lines 17 through 20. The Application-as-filed additionally discloses that linear polymers suitable for use in the instant invention may have a molecular weight of 5 000 g/mol, as described in the Application-as-filed on Page 2, line 20.

Applicants thus respectfully submit that the Application-as-filed clearly conveys with reasonable clarity to one skilled in the art that Applicants were in possession of the claimed invention as of the filing date sought. More specifically, one skilled in the art would consider the claimed lower end point of 5 000 and upper end point of 10 000 000 g/mole and all molecular weights between the lower and upper end points to be expressly supported by the discussion in the original disclosure. Applicants likewise further respectfully submit that one skilled in the art would consider the claimed range supported by the original disclosure in conformance with *In re Wertheim*, 541 F.2d 257 (CCPA 1976) (MPEP 2163.05). Accordingly, Applicants respectfully request withdrawal of the foregoing rejection.

Claims 20 and 21 apparently stand rejected over the recitation "20-arm." Claims 20 and 21 have been amended to remove the term "20-arm." Applicants' Representative respectfully submits that support was taken for the foregoing term from the Application-as-filed on Page 24, line 18, noting "Example 1: [PEI/$(PEG)_{20}$]." Solely to advance

prosecution, the foregoing term has been cancelled from Claims 20 and 21. Accordingly, Applicants request withdrawal of this rejection.

The Claimed Invention is Patentable in Light of the Art of Record

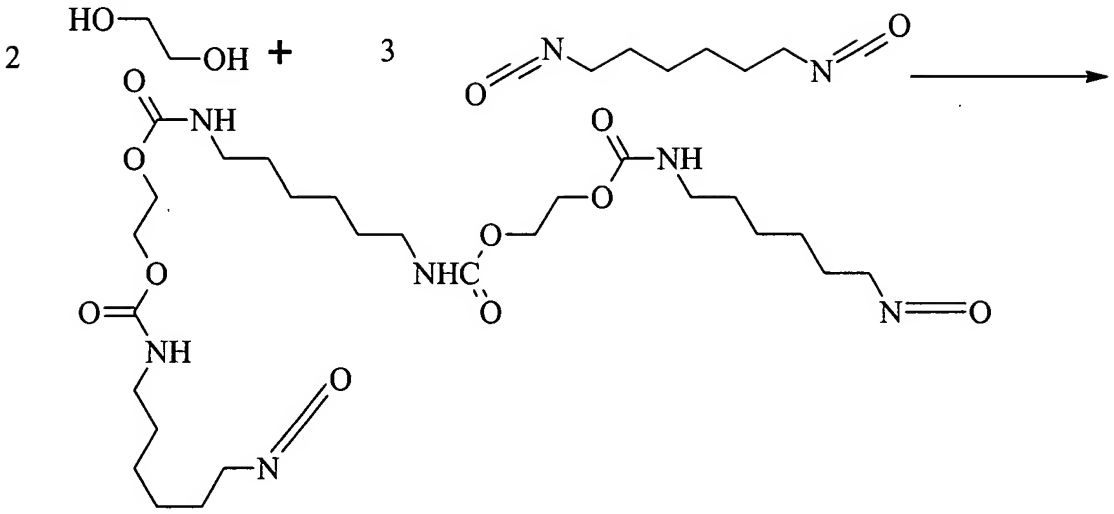
Claims 1 through 3, 6, 8, 23 and 24 stand rejected as anticipated by United States Patent 5,204,196 to Yokomichi et al.

Claims 1 through 3, 6, 8, 10 through 13 and 19 stand rejected as anticipated by WO 9859064, whose English equivalent is United States Published Application 2001/0005717 to Wagner et al.

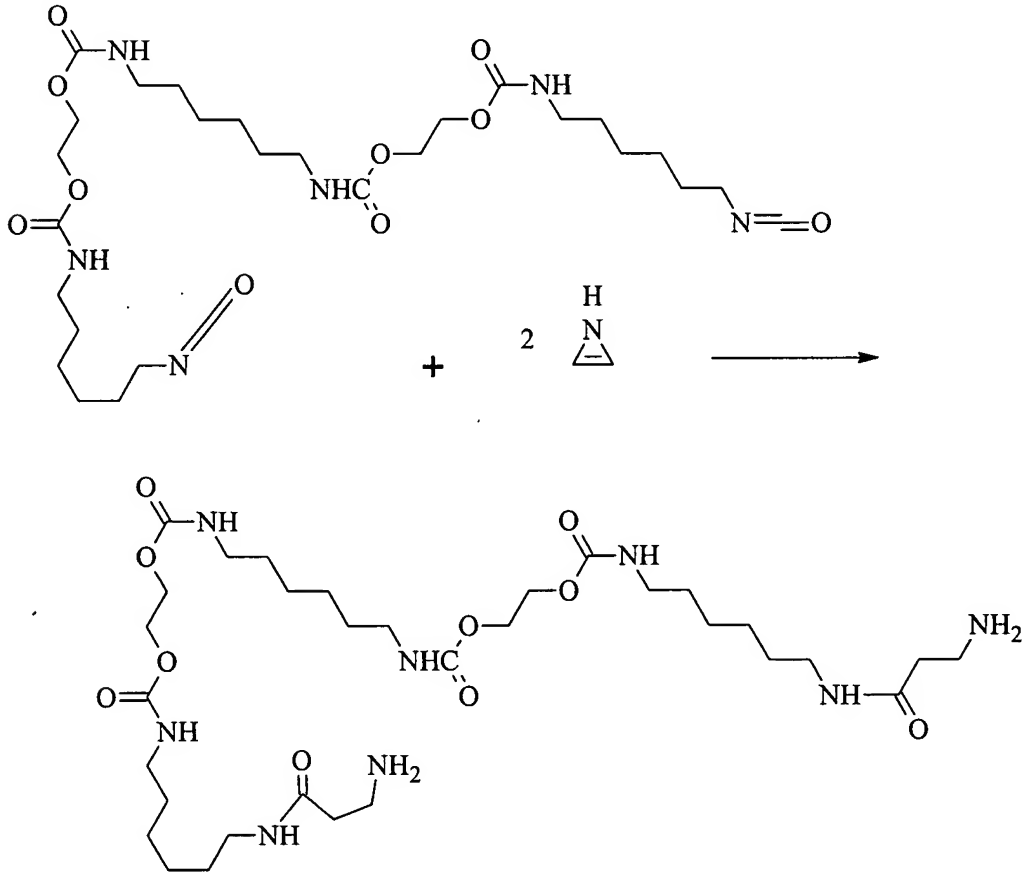
Claims 10 through 13 and 19 stand rejected over Yokomichi in view of Ogris et al. in Gene Therapy, Vol. 6, Issue 4, April 1999, Pages 595 – 605. (Gene Therapy)

It may be useful to briefly consider the invention before addressing the merits of the rejection.

The synthesis for the claimed compounds claimed starts with a polyethylene glycol "A". This compound is reacted with a linker compound providing the linker "X" for instance with a diisocyanate as indicated below.



The substance thus obtained is subsequently treated with an ethyleneimine "B" or a polyethyleneimine "B." The reaction sequence is as follows:



Applicants respectfully submit that the cited references do not teach or suggest the claimed invention.

Yokomichi Does Not Teach or Suggest the Recited Balance of Charges in the Compounds Synthesized

Applicants respectfully submit that if a higher ratio of ethyleneimine or polyethyleneimine than indicated is used, this will introduce positive charges in the polymer. The number of positive charges will depend on the amount of nitrogen compound added. These positive charges have to be balanced by a selected amount of negative charges. Merely adding an unknown amount of sodium hydroxide having a concentration of 100 g/l, as indicated in example 1 of Yokomichi, will not be sufficient as it might be to much thus creating a net negative charge on the molecule synthesized or to less leaving some positive charges on the molecule.

Furthermore, the sodium hydroxide in Yokomichi's Example 1 is not used to obtain a polyethyleneimine polyethylene glycol copolymer wherein the two moieties are connected via a diurethane linker coming from a diisocyanate. The alkali hydroxide (100 g/l) of Yokomichi is rather needed to hydrolyze poly-N-acetyleneimine into the free polyethyleneimine (cf. US 196, column 3, l. 39 to 46; column 4, l. 65 to 67). This is prior to synthesizing the copolymers. Thus the hydroxide cited within the outstanding Office Action at Paragraph 5 is not involved in balancing charges in polyethylene glycol diisocyanate polyethyleneimeine copolymers.

Applicants further respectfully submit that the copolymer synthesized in Example 1 of Yokomichi is precipitated with an amount of $LiClO_4$ such that the final concentration of $LiClO_4$ in the copolymer/salt composition is 18.6 percent by weight (or 19 percent by weight for the six polymer/salt compositions in Example 3). This defines a definite number of charges provided from the salt in whatever the polymer composition will be. However, the different polymers obtained are differently charged due to a changing

amount of polyethyleneimine. Furthermore the solvent used during polymerization also seems to influence the overall charge and conductivity characteristics of the polymer, as can be gleaned from Example 4 (cf. US 196, column 5, l. 36 to 41).

Accordingly, Applicants respectfully submit that Yokomichi, teaching a set amount of $LiClO_4$ with varying amounts of polyethyleneimine and differing solvents, does not teach or suggest the recited balanced charges. Nor does Yokomichi provide one skilled in the art with any guidance as to the balancing of charges in the differently charged polymers synthesized by merely adding a definite, set amount of $LiClO_4$.

Applicants respectfully submit that the recited feature of balanced charges is highly advantageous when complexing DNA. Carboxylic acids for instance behave completely different when charged or when protonated. This also applies for the compounds of the invention and is even more pronounced as the number of charges is much higher compared to a simple carboxylic acid.

Based upon the foregoing, Applicants respectfully submit that the recited balanced charge is not taught or suggested by Yokomichi.

Yokomichi Further Does Not Teach or Suggest the Recited Hydrophilic Polymer with a Minimum Molecular Weight of 5000 g/mol

Applicants respectfully submit that the Examiner correctly defines the degree of polymerization is, viz. the ratio of the molecular weight of the polymer divided by the molecular weight of the monomer forming said polymer.

The monomer of a polyethylene glycol is ethylene oxide or ethylene glycol and not a polyethylene glycol which is already a polymer, as further urged within the Office Action, however. The Office Action is more particularly incorrect in its identification of

a polyethylene glycol as "monomer" which is then deemed to polymerize to another polyethylene glycol of a much higher weight.

Applicants respectfully submit that it is not possible to get polyethylene glycols to per se polymerize. The polyethylene glycol has to be activated, for instance by a diisocyante (cf. reaction schemes supra). If one uses such activation step, the polymerized polyethylene glycol will not give another polyethylene glycol with an even higher degree of polymerization, but a copolymer of diisocyanate and polyethylene glycol or of diisocyanate, polyethylene glycol and polyethyleneimine, provided the last compound is in the reaction mixture (cf. column 2, l. 9-23 of Yokomichi).

Hence polymers having a polyethylene glycol portion with a molecular weight of 550 g/mol are not disclosed in Yokomichi to give a molecular weight of 6,490 g/ml when multiplied by the polymerization degree of 11.8 as urged within the Office Action. They will instead form a copolymer as indicated above.

This can be clearly seen from the section "Synthesis of Solid State and Conductive Polymer Composition" of Example 1 of Yokomichi. They use a polyethylene glycol monomethylether having an average molecular weight of 550 g/mol and an average polymerization degree of 11.8. The methoxy-group of this compound makes 31 g/mol. and thus 550 g/mol – 31 g/mol should give the molecular weight of polyethylene moiety without methoxy which is 519 g/mol. This moiety bears a hydrogen atom at the terminal oxygroup thus giving 520 g/mol (519 plus 1). However, 520 g/mol divided by 11.8 yields 44 g/mol which is the molar weight of the monomer ethylene oxide ($-CH_2-CH_2-O-$).

The same calculation applies for the monomethylether of polyethylene glycol with a molecular weight of 350 g/mol and a degree of polymerization of 7.2 as disclosed in example 3 of Yokomichi.

Applicants thus respectfully submit that the Office Action's assertion that the compounds disclosed in Yokomichi have a molecular weight of 6,490 g/mol is not correct because:

- PEO-polymers having a molecular weight of 550 g/mol (cf. example 1) undergo reactions with a diisocyanate which would lead to polyethylene glycol diisocyanate copolymers and not to polyethylene glycols of higher molecular weight.

- Calculation clearly shows that the polymerization degrees of 11.8 and 7.2 refer to the polymerization degree of the starting material, viz. the polyethylene glycol monomethylether and not to a compound which may be obtained from said starting material. The starting material is not a monomer and cannot be considered as such.

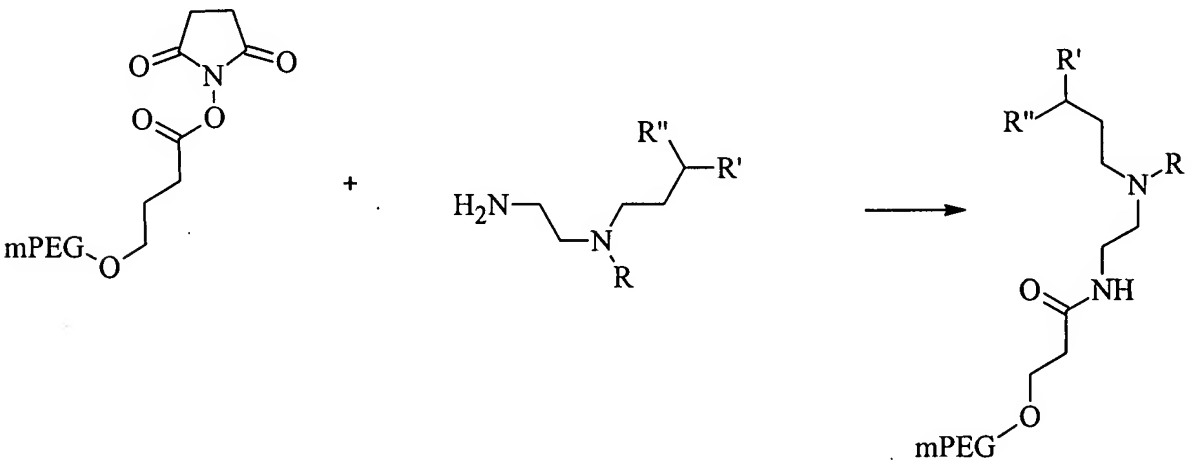
- This also fits with indications in the formula disclosed in the abstract and in column 1 of Yokomichi wherein "m" comprises values ranging from 3 to 100. When one assumes 44 g/mol to be the molar weight of $-CH_2-CH_2-O-$, which can be found "m" times in the copolymers of Yokomichi, the highest molecular weight of the polyethylene oxide portion can be is 4,400 g/mol and not 6,490 g/mol, as urged within the Office Action.

Based upon the foregoing, Applicants respectfully submit that the recited hydrophilic, non-ionic polymer having a minimum molecular weight of 5000 g/mol is clearly not taught or suggested by Yokomichi.

Accordingly, Applicants respectfully submit that the claimed invention is patentable in light of Yokomichi, considered either alone or in combination with the art of record.

Wagner Likewise Does Not Teach or Suggest the Recited Balance of Charges in the Compounds Synthesized

Applicants respectfully submit that m-PEG-SPA (= methoxy-polyethylene glycol succinimidyl-propionate, not methoxy-succinimidyl-propionate as stated within the Office Action) will not conserve its anionic character and does not stabilize polyethyleneimine in complex union with polyethylene glycol, in contrast to the urgings in Paragraph 7 of the outstanding Office Action. The reaction mechanism is as follows, and is also provided in the technical article entitled *Development of Pegylated Interferons for the Treatment of Chronic Hepatitus C*, BioDrugs 2001: 15(7); 419 – 419, Kozlowski et al, attached as Exhibit I.



The succinimid group is a good leaving group and makes the activated methoxy-polyethylene glycol propionic acid accessible to polyethyleneimines, which then undergo a reaction with the activated propionic acid moiety to give the corresponding amide which is a covalent compound and not a complex of charged entities (as inferred by the outstanding Office Action). More specifically, the propionate does not have a charge or any anionic character, as indicated above. This is in contrast to the opinion urged at Paragraphs 7 and 8 of the Office Action, which incorrectly indicates that the "methoxy-succinimidyl-proprionate" serves as an anionic component.

Applicants thus respectfully submit that free (and thus charged) propionate never appears during the whole reaction of coupling methoxy polyethylene glycol succinimidyl propionate and polyethyleneimine within Wagner. Therefore, no negative charges resulting from said propionate can be found to stabilize positive charges of polyethyleneimine.

Consequently methoxy polyethylene glycol succinimidyl propionate can not compensate charges of polyethyleneimine by complexing with it, as the bond between these two entities is instead covalent (cf. also example 2 of US 717, para 0087 right side).

The Office Action is further incorrect in its urging that the hydroxyl anions present in water balance positive charges of the compounds of the invention. Every aqueous sample contains hydroxyl anions to a very small extent. One has however to take into account that these aqueous samples have a pH of 7 viz. the concentration of protons and of hydroxyl ions is 10^{-7} each, which is very small and too small to equal the amount of positive charges in the compounds of the invention. Furthermore, Wagner prefers using MQ-water containing no salt and thus having no charges, to avoid aggregation of polymer/DNA-complexes (cf. US 717, page 3 sections 0038 and 0039 and figure caption 1 on page 4). He would never do so, if charges of hydroxyl ions in MQ water were detrimental.

Applicants thus respectfully submit that the Office Action's statement that Wagner disclose anions coming from the propionate moiety of methoxy polyethylene glycol succinimidyl propionate is not correct. Applicants further respectfully submit that hydroxyl anions are also not provided in a concentration necessary for making a counter part to the positive charges in the compounds of the invention.

Accordingly, the recited balance of charges in order to achieve neutrality is not taught or suggested by Wagner.

To the contrary, Wagner notes that coupling of polyethylene glycol to positively charged DNA/polylysine complexes reduces the activation of the complement system, which is to say that even charged DNA/polymer complexes show an effect regarding the impact on the immune system. (US 717, Page 1, Paragraph 0013).

Consequently, balancing charges is not at all in the scope of Wagner, as Wagner discloses on Page 3 sections 0038 and 0039 and in Figure Caption 1 on Page 4 to instead reduce or completely avoid the presence of salts (i. e. charges) in the preparations in order to diminish polymer/DNA-complex aggregation.

Further evidence of Wagner's charge avoidance is provided in Wagner's Example 2b conducted in DMSO and in MQ-water, which both are free of charges. Even the added glycine (only 200 nmol/l), which has a zwitterionic character, is not used to balance the charges on the copolymer synthesized, but rather to remove the excess of m-PEG-SPA, viz. to transform the excess of activated propionic acid moieties therein to amides thus stopping the pegylation reaction.

Wagner, disclosing the reduction or entire elimination of charges, does not teach or suggest balancing them. Thus Wagner does not teach or suggest the recited "moiety $[A^-]_w$ where $[A^-]$ is an equivalent of an anion and w is an integer selected to balance the positive charges in the polyethyleneimine (PEI)."

Wagner further does not teach or suggest DNA contacted with a complex of PEG and PEI

Applicants respectfully submit that Wagner's Claim 24 and all examples except for one disclose PEI to be contacted with DNA to form a complex and only thereafter is the complex is reacted with m-PEG-SPA. Thus for the majority of the examples, copolymers comprising polyethyleneimine and polyethylene glycol are not disclosed, but are instead complexes of polyethyleneimine and DNA.

The only exception is Wagner's Example 2b, in which the copolymer methoxy polyethyelene glycol propioamido polyethyleneimine as indicated in the figure above is contacted with DNA to form a complex. This is a complex between the copolymer and DNA, but not a complex between polyethyleneimine and polyethylene glycol, as these two latter polymers are covalently connected and thus form one unique compound as already mentioned.

Accordingly, Applicants respectfully submit that the claimed invention is patentable in light of Wagner, considered either alone or in combination with the art of record.

Claims 10 to 13 and 19 are Likewise Patentable in light of Yokomichi in combination with Ogris

Applicants respectfully submit that Yokomichi and Ogris, considered either alone or in combination, both fail to teach or suggest (i) the recited polyethylene glycols having a molecular weight equal or higher than 5,000 g/mol and (ii) polyethyleneimines comprising a moiety $[A^-]_w$ where $[A^-]$ is an equivalent of an anion and w is an integer selected to balance the positive charges in the polyethyleneimine (PEI).

Ogris merely discloses complexes of polyethyleneimine and DNA: "PEGylation of the complexes strongly reduces plasma protein binding...". This shows that a complex of DNA and polyethyleneimine is PEGylated but not free polyethylene itself. Applicants respectfully submit that if a complex such as provided in Ogris is PEGylated, the PEGylation can also take place at various positions of the DNA, in particular at the hydroxyl groups of desoxyribose. In addition, DNA-charged polyethyleneimine itself will certainly be differently PEGylated than the free polyethyleneimine itself. The molecules thus obtained are thus altogether different from the compounds of the invention.

Accordingly, Applicants respectfully submit that Claims 10 to 13 and 19 are patentable in light of Yokomichi in combination with Ogris.

Cancellation of Withdrawn Claims

In conformance with United States practice, Claim 14 and 15 have been canceled solely to advance prosecution of the above referenced case, as required in Paragraph 14 of the outstanding Office Action to ensure a "complete" reply to the final rejection. Applicants respectfully reiterate that Claims 14 and 15 have been canceled without prejudice or disclaimer to the filing of continuing applications thereon.

CONCLUSION

It is respectfully submitted that Applicants have made a significant and important contribution to the art, which is neither disclosed nor suggested in the art. It is believed that all of pending Claims 1 through 3, 6, 8, 10 through 13 and 19 through 24 are now in condition for immediate allowance. It is requested that the Examiner telephone the undersigned if any questions remain to expedite examination of this application.

It is not believed that extensions of time or fees are required, beyond those which may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time and/or fees are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required is hereby authorized to be charged to Deposit Account No. 50-2193.

Respectfully submitted,

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